44. (new) The method as claimed in claim 40, wherein said enhanced natural killer cell response is evaluated by an *in vitro* assay comprising:

(a) contacting natural killer cell-sensitive target cells with effector cells, wherein said effector cells are from said individual that has been administered said composition;

(b) determining the level of lysis of said natural killer cell-sensitive target cells; wherein increased lysis of natural killer cell-sensitive target cells contacted with effector cells from said individual that has been administered said composition as compared to natural killer cell-sensitive target cells contacted with effector cells from an individual that has not been administered said composition indicates an enhanced natural killer cell response.

REMARKS

Claims 31, 33-38, 40, and 44 are pending. Claims 32, 39, and 41 have been canceled. Claims 31, 33-38, and 40 have been amended. Claim 44 has been added. Support for the amended and new claims may be found in the specification. Specifically, support for claims 31 can be found on page 5, lines 11-15; page 7, line 22 to page 8, line 13; page 23, line 15 to page 24, line 18; and page 31, lines 5-11 of the instant specification. Support for claim 33 can be found on page 5, lines 11-15 and on page 8, line 14 to page 9, line 13 of the instant specification. Support for claim 34 can be found on page 10, lines 15-19 of the instant specification. Support for claims 35-36 can be found on page 5, lines 11-15 and page 7, lines 22 to page 8, line 13 of the instant specification. Support for claims 37-38 can be found on page 6, lines 13-15 of the instant specification. Support for claim 40 can be found on page 22, lines 13-15 of the instant specification. Support for claim 44 can be found on page 18, lines 6-20; page 30, line 1-2; page 31, lines 5-11; and page 33, line 15 to page 34, line 8 of the instant specification. Thus, the claim amendments and new claim do not introduce new matter.

A marked up version of the amended claims showing the amendments is attached hereto as Appendix A. Matter that has been deleted is indicated by brackets and matter that has been added is indicated by underlining. A copy of the claims as pending after entry of the foregoing amendment is attached as Appendix B. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present application.

The Rejections Under 35 U.S.C. § 112, First Paragraph Should Be Withdrawn

Claim 31 is rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention at the time the application was filed. The Examiner contends that the specification fails to teach the use of saponins from sources other than *Quillaja saponaria*. Accordingly, without in any way conceding that this subject matter in question is not described by the specification and for the sole purpose of expediting prosecution of this application and with fully reserving our rights to prosecute this subject matter in a subsequent patent application, Applicant has amended claim 31. Currently pending claim 31 now specifies that the saponin used in the methods of the invention is a *Quillaja saponaria* saponin.

The Examiner alleges that the specification only teaches QS-21 and QS-7 saponin isolated from *Quillaja saponaria* purified by HPLC. Applicant respectfully disagrees with the Examiner's position that the specification fails to teach other *Quillaja saponaria* saponins or biologically active fragments or chemically modified species thereof. For example, the specification clearly discloses QS-7, QS-17, QS-18, and QS-21 as saponins that can be used in the methods of the invention (see *e.g.*, 5, lines 11-15 of the instant specification) as well as references which describe methods of purification (see *e.g.*, page 8, lines 3-13). Additionally, modified saponins and methods of making such saponins are clearly described in the specification (see *e.g.*, page 8, line 14 to page 9, line 13). The Examiner appears to be positing a rule that an Applicant must be limited to claiming only what is present in the working examples. This is not the law. In fact, there is no requirement that an application have any working examples, even when the invention involves a complex technology. See In re Strahilevitz, 668 F.2d 1229, 212 U.S.P.Q. 561 (C.C.P.A. 1982). Therefore, the fact that Applicant does not have experimental data using each and every *Quillaja saponaria* saponin taught in the specification is not material to patentability.

Claims 31-41 are rejected under 35 U.S.C. § 112, first paragraph because the specification allegedly does not provide enablement for a method of stimulating an innate immune response by administering any saponin to an individual other than a mouse.

Applicant has amended the claims to reflect the that *Quillaja saponaria* saponins are to be used in the methods of the invention. As such, the class of saponins does not have the breadth objected to by the Examiner. In fact, the Examiner admits that the instant

specification is enabled for administration of *Quillaja saponaria* saponins (see page 4, lines 14-15 of the Office Action mailed October 23, 2002).

The Examiner, however, maintains that the specification is only enabled for stimulating innate immunity in a mouse rather than any individual. Applicant respectfully disagrees. The Examiner's attention is directed to the opinion of the Court of Appeals for the Federal Circuit (C.A.F.C.) in In re Brana, 5 F.3d 1557, 34 U.S.P.Q.2d 1437 (Fed. Cir. 1995) that the testing for the full safety and effectiveness of a product is more properly left to the Food and Drug Administration and the requirements under the law for obtaining a patent should not be confused with the requirements for obtaining government approval to market a particular drug or therapeutic method for public use. Id. at 1442. Thus, Applicant is not under an obligation to detail the full effectiveness in individuals other than mice in order to enable the claimed methods. Demonstration of proof of principle in an accepted mammalian model system (*i.e.*, the mouse) is enough to enable the present claims.

In view of the foregoing, Applicant requests that the Examiner withdraws the rejections under 35 U.S.C. §112, first paragraph.

The Rejections Under 35 U.S.C. § 112, Second Paragraph Should Be Withdrawn

Claims 32-41 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention.

The Examiner contends that the word "derived" renders the claims 32-41 indefinite. Applicant has amended the claims and, as such, the rejection has been obviated.

The Examiner contends that the recitation of "wherein the saponin is modified" renders claim 33 indefinite. One of ordinary skill in the art understands the term "modified" as used in the above-mentioned claim and in the present specification to be a chemical modification that alters the structure of the saponin. For example, the specification incorporates by reference a number of references which teach chemically modified saponins that are known in the art (see *e.g.*, page 8, line 14-page 9, line 13 of the instant specification). For example, as taught in Kensil, U.S. Patent No. 5,443,829, *Quillaja saponaria* Molina saponins can be chemically modified by subjecting them to a mild reducing agent such that the aldehyde group of the saponins are reduced to yield the corresponding alcohol. Additionally, Kensil et al., U.S. Patent No. 5,583,112, teaches that the carboxyl group on the glucuronic acid of saponins from *Quillaja saponaria* Molina can

be conjugated to a protein, a peptide, or a small molecule containing a primary amine. Marciani et al., U.S. Patent No. 5,977,081, also discloses chemically modified saponins such as those in which the carboxyl group on the glucuronic acid of nonacylated or deacylated saponins from *Quillaja saponaria* are conjugated to a lipid, fatty acid, polyethylene glycol, or terpene. Thus, a mere mixing of a saponin with a pharmaceutical carrier or dissolution of a saponin in a solvent are not modifications as that term is used in the specification, or as the term is generally understood by one of skill in the art. However, Applicant has amended the claim to recite "chemically modified" to more particularly point out and distinctly claim the invention.

The Examiner contends that the recitation of "further enhances a natural killer cell response in a positive synergistic manner" renders claim 41 indefinite. Applicant has canceled claim 41 thus obviating the rejection.

The Examiner contends that claims 31-41 are incomplete for omitting the allegedly essential step of how to determine whether an innate immune response is stimulated in an individual. Unclaimed subject matter is essential only if the specification indicates so. Whether or not matter is essential is not a determination for the Examiner to make, but rather is made by the Applicant and set out in their specification.

> A claim which omits matter disclosed to be essential to the invention as described in the specification or in other statements of record may be rejected under 35 U.S.C. 112, first paragraph, as not enabling. In re Mayhew, 527 F.2d 1229, 188 U.S.P.Q 356 (C.C.P.A. 1976).

M.P.E.P. § 2172.01 (Rev. 1, Feb. 2000) (and the cases cited therein) (emphasis added). Further, a related section of the M.P.E.P. states the following:

> In determining whether an unclaimed feature is critical, the entire disclosure must be considered. Features which are merely preferred are not to be considered critical. In re Goffe, 542 F.2d 564, 567 (C.C.P.A. 1976).

M.P.E.P. § 2164.08(c) (Rev. 1, Feb. 2000) (also suggesting an enablement rejection in the case of unclaimed subject matter).

Applicant respectfully submits that the Examiner has not met the burden of establishing a *prima facie* case of unclaimed, essential subject matter. Matter is "essential" only if the specification so indicates. But, here, the Examiner has not cited to any portions

of the specification, much less to any portions indicating that certain matter not claimed was deemed essential by the Applicant to her invention. Respectfully, the Examiner's contention that the alleged omitted steps are unclaimed essential matter is only speculation in the absence of any support in the specification that the subject matter is essential. Therefore, the required *prima facie* case has not been established and the omitted steps have not been shown to be essential.

The pending claims relate to treating cancer by stimulating innate immunity by administration of a *Quillaja saponaria* saponin. The test of definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. Orthokinetic Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565, 1 U.S.P.Q.2d 1081 (C.A.F.C. 1986). Applicant contends that this standard has been met by the pending claims. One skilled in the art could measure innate immunity stimulation using any method known in the art. In addition to providing working examples demonstrating one known method with which to measure innate immunity stimulation (*e.g.*, ^{51}Cr release lysis assay on page 33, line 14 to page 34, line 8 of the instant specification), the specification also provides teachings pertaining to additional methods (see *e.g.*, 18, lines 6-20) as well as examples of specific types of biological responses that indicate such a stimulation such as induction of cytokines, proliferation, or lytic response (see *e.g.*, page 17, lines 7-8 and page 18, lines 2-5 of the instant specification). Applicant points out that the exact method used to determine innate immunity stimulation is unimportant - - only that innate immunity is stimulated is relevant.

In view of the foregoing, Applicant requests that the Examiner withdraws the rejections under 35 U.S.C. §112, second paragraph.

The Rejection Under 35 U.S.C. § 102 Should Be Withdrawn

Claims 31-34, 37, 39, and 40 are rejected under 35 U.S.C. § 102(b) as being anticipated by Chavali et al., 1987, *Immunobiol.* 174:347-59 ("Chavali"). The Examiner alleges that Chavali discloses *Quillaja saponaria* saponin enhanced natural killer cell activity in mice. Applicant contends that, as amended, the claims are not anticipated by Chavali.

The pending claims relate to treating cancer by stimulating innate immunity by administration of a *Quillaja saponaria* saponin or purified component thereof. Chavali

does not disclose administering *Quillaja saponaria* saponin to an individual suffering from cancer to treat the disorder.

In order for a reference to anticipate a claim, each and every element of the claim must be disclosed in that one reference. Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 1 U.S.P.Q.2d 1081 (Fed. Cir. 1985). "Anticipation under Section 102 can be found only if a reference shows exactly what is claimed. . . ." Structural Rubber Prod. Co. v. Park Rubber Co., U.S.P.Q. 1264 (Fed. Cir. 1984). If it is necessary to reach beyond the boundaries of a single reference to provide a missing disclosure of the claimed invention, it is not a § 102 anticipation. Scripps Clinic & Research FDN. v. Genentech Inc., 927 F.2d 1565, 18 U.S.P.Q.2d 1869 (Fed. Cir. 1991). Furthermore, anticipation is not shown even if the differences between the claims and the prior art reference are argued to be "insubstantial" and the missing elements could be supplied by the knowledge of one skilled in the art. Structural Rubber Prod. Co. v. Park Rubber Co., 221 U.S.P.Q. 1264 (Fed. Cir. 1984).

In view of the foregoing, Applicant requests that the Examiner withdraws the rejection under 35 U.S.C. §102.

The Rejections Under 35 U.S.C. § 103 Should Be Withdrawn

Claims 35-36 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Chavali in view of U.S. Patent No. 6,231,859 by Kensil ("Kensil"). The Examiner alleges that one of skill in the art would be motivated to combine the teachings of Chavali and Kensil to use purified *Quillaja saponaria* saponins to enhance natural killer cell activity in mice. Applicant contends that, as amended, the claims are made obvious by Chavali and Kensil.

The pending claims relate to treating cancer by stimulating innate immunity by administration of a *Quillaja saponaria* saponin or purified component thereof. Neither Chavali nor Kensil teach or suggest administration of any *Quillaja saponaria* saponin for the treatment of cancer.

A finding of obviousness under 35 U.S.C. § 103 requires a determination of the scope and the content of the prior art, the differences between the invention and the prior art, the level of the ordinary skill in the art, and whether the differences are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Graham v. Deere, 383 U.S. 1 (1966). The relevant inquiry is whether the prior art suggests the invention, and whether one of ordinary skill in

the art would have had a reasonable expectation that the claimed invention would be successful. In re O'Farrell, 853 F.2d 894, 902-4 (Fed. Cir. 1988); In re Vaeck, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991). Both the suggestion of the claimed invention and the expectation of success must be in the prior art, not in the disclosure of the claimed invention. In re Dow Chemical Co., 5 U.S.P.Q. 2d 1529 (Fed. Cir. 1988).

In view of the foregoing, Applicant requests that the Examiner withdraws the rejections under 35 U.S.C. §103.

Claim Objections

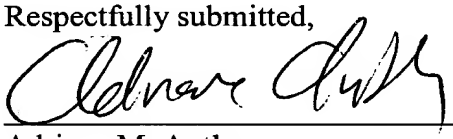
Claim 40 was objected to for failing to further limit the parent claim. Applicant has amended the claim such that it is now in proper form.

CONCLUSION

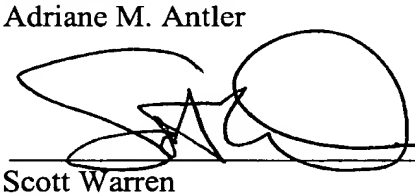
Applicant respectfully requests that the amendments and remarks made herein be entered and made of record in the file history of the present application. Withdrawal of the Examiner's rejections and a notice of allowance are earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

Date: April 23, 2003



Adriane M. Antler — 32,605 (Reg. No.)

By: 

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APPENDIX A
MARKED-UP VERSION OF AMENDED CLAIMS
U.S. PATENT APPLICATION SERIAL NO. 09/760,506
ATTORNEY DOCKET NO. 8449-153-999

31. (amended) A method of treating cancer [for stimulating innate immunity] comprising administering to an individual in need thereof an effective amount of a composition comprising a *Quillaja saponaria* saponin, wherein said effective amount stimulates innate immunity [to an individual].

33. (amended) The method as claimed in claim [32] 31, wherein [the] said *Quillaja saponaria* saponin is chemically modified.

34. (amended) The method as claimed in claim [32] 31, wherein [the] said *Quillaja saponaria* saponin [comprises a] is substantially pure [saponin].

35. (amended) The method as claimed in claim 34, wherein [the] said substantially pure *Quillaja saponaria* saponin [comprises] is QS-7, QS-17, QS-18, or QS-21.

36. (amended) The method as claimed in claim 35, wherein [the] said substantially pure *Quillaja saponaria* saponin [comprises] is QS-21.

37. (amended) The method as claimed in claim [32] 31, wherein said individual is [the composition stimulates an innate immune response when administered to] a mammal.

38. (amended) The method as claimed in claim [32] 31, wherein said individual is [the composition stimulates an innate immune response when administered to] a human.

40. (amended) The method as claimed in claim [32] 31, wherein [the method further] said effective amount of a composition comprising a *Quillaja saponaria* saponin is an amount sufficient to enhances a natural killer cell response.

APPENDIX B
PENDING CLAIMS AS OF APRIL 23, 2003
U.S. PATENT APPLICATION SERIAL NO. 09/760,506
ATTORNEY DOCKET NO. 8449-153-999

31. (amended) A method of treating cancer comprising administering to an individual in need thereof an effective amount of a composition comprising a *Quillaja saponaria* saponin, wherein said effective amount stimulates innate immunity.

33. (amended) The method as claimed in claim 31, wherein said *Quillaja saponaria* saponin is chemically modified.

34. (amended) The method as claimed in claim 31, wherein said *Quillaja saponaria* saponin is substantially pure.

35. (amended) The method as claimed in claim 34, wherein said substantially pure *Quillaja saponaria* saponin is QS-7, QS-17, QS-18, or QS-21.

36. (amended) The method as claimed in claim 35, wherein said substantially pure *Quillaja saponaria* saponin is QS-21.

37. (amended) The method as claimed in claim 31, wherein said individual is a mammal.

38. (amended) The method as claimed in claim 31, wherein said individual is a human.

40. (amended) The method as claimed in claim 31, wherein said effective amount of a composition comprising a *Quillaja saponaria* saponin is an amount sufficient to enhances a natural killer cell response.

44. (new) The method as claimed in claim 40, wherein said enhanced natural killer cell response is evaluated by an *in vitro* assay comprising:

(a) contacting natural killer cell-sensitive target cells with effector cells, wherein said effector cells are from said individual that has been administered said composition;

(b) determining the level of lysis of said natural killer cell-sensitive target cells; wherein increased lysis of natural killer cell-sensitive target cells contacted with effector cells from said individual that has been administered said composition as compared to natural killer cell-sensitive target cells contacted with effector cells from an individual that has not been administered said composition indicates an enhanced natural killer cell response.